REMARKS

In paragraph 2 of the Action, claims 25-31 were rejected under 35 U.S.C. 102(b) as being anticipated by JP 11-299901.

In view of the rejection, claim 25 has been amended, and new claim 79 has been filed. Claims 27, 28 and 30 have been editorially amended.

A process of producing a stent of claim 25 comprises the steps of preparing a tubular stent matrix extendable in a diametric direction, forming flexible solid polymer layers on said stent matrix to cover entire inner and outer surfaces of the stent matrix, and then perforating a plurality of fine through pores in the solid polymer layers at portions only where the stent matrix does not exist.

In the above steps, the forming the solid polymer layers comprises a step of installing the stent matrix on an inner polymer layer disposed on an outer surface of a mandrel; a step of forming an outer polymer layer by impregnating the mandrel into a liquid resin material for forming the outer polymer layer and pulling up the mandrel; and a step of equalizing the thickness of the outer polymer layer by pulling up the mandrel in a vertical direction and controlling a pulling-up speed.

Namely, in forming the solid polymer layers, the inner polymer layer is disposed on the outer surface of the mandrel, and the stent matrix is installed on the inner polymer layer. Then, the mandrel with the inner polymer layer and the stent matrix is impregnated into the liquid resin material and pulled up to form the outer polymer layer. After the inner and outer polymer layers are formed on the stent matrix, the fine through pores are formed at the polymer layers where the stent matrix does not exist.

In the Action, paragraph 0016 of JP '901 was referred to for the disclosure such that forming the layers comprises a step of

forming a polymer film by impregnating a mandrel into a liquid resin material. However, what is disclosed in paragraph 0016 is the material for the flexible polymer film, such as high molecular elastomer. In paragraph 0016, it is not disclosed or suggested that the polymer film is formed by impregnating a mandrel into a liquid resin material.

In the Action, paragraph 0033 of JP '901 was also referred to for the disclosure of equalizing the thickness of the polymer film by pulling up on the mandrel in a vertical direction. However, in paragraph 0033, it is stated that a mandrel 22 for a cover strip is impregnated into a polymer liquid 26, and after the polymer is coated on the entire outer surface of the mandrel, the mandrel is pulled up. The equalizing the thickness of the polymer film is not explained in this section.

In JP '901, after the mandrel for the cover strip is impregnated into the polymer liquid (Fig. 7(a)), the mandrel is dried and formed with pores (Fig. 7(b)), and the mandrel is removed to thereby form the cover strip (Fig. 7(c)). A stent is supported (Fig. 7(d)), and the stent is put into the cover strip while the cover strip is sufficiently opened by blowing air into the cover strip (Fig. 7(e)). The air supply is stopped and the cover strip is allowed to shrink, and then, the cover strip with the stent is cut (Fig. 7(f)).

JP '901 cited in the Action is explained in the original specification. Especially, as explained in paragraph 0008 of the specification, in JP '901, an inner periphery of the stent matrix is not covered with a polymer film, so that the metallic stent matrix is exposed to the blood. Thus, there is a problem of causing thrombus, allergic to metal, stimulus of tissues due to metal and rust development. Especially, since the inner periphery of the stent has convexes formed by stent struts composing the stent

matrix, the convexes disarrange bloodstream, facilitating the formation of thrombus. The formed thrombus exfoliates and moves downstream (travel through the bloodstream) to cause infarction on the small blood vessel on the downstream side or platelet derived growth factor discharged from blood platelets in the thrombus stimulates to cause thickening. Therefore, the problem of causing intimal thrombus is serious at this portion.

In JP '901, the stent matrix is simply inserted into the cover film, and the cover is merely shrunk, to thereby form the polymer film on the outer surface of the stent matrix. In this structure, the polymer film is not united with the stent matrix sufficiently. Thus, the polymer film may have a chance to move over the stent matrix.

Also, in JP '901, after the fine pores are formed in the cover film, the stent is inserted into the cover film. Therefore, the fine pores may be closed by the stent matrix, so that the fine pores may not be sufficiently used.

As explained above, if the outer surface of the stent is only covered by the polymer film, thrombus may be formed in the blood vessel. This fact is explained in the Article "DEVELOPMENT OF MICROPOROUS COVERED STENTS" by Nakayama et al. (The International Journal of Artificial Organs/Vol. 28/no. 6, 2005/pp. 600-808), as attached herewith. In this article, the stent made according to the conventional method such as JP '901 and the stent of the present invention are compared. The disadvantages of the conventional stents are recognized in this article.

As explained above, the features of the invention are not disclosed or even suggested in JP '901.

Claims pending in the application are patentable over JP '901.

Reconsideration and allowance are earnestly solicited.

If any further amendment or clarification is required, please contact the undersigned agent.

Respectfully Submitted,

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Artificial Heart and Cardiac Assist Devices

Development of microporous covered stents: Geometrical design of the luminal surface

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ABSTRACT: To reduce in-stent restenosis rates we have developed newly designed covered stents, in which a stent strut is buried into a microporous elastomeric cover film to provide a physical barrier against tissue ingrowth and a pharmacological reservoir for drug-eluting.

The covered stents were prepared by dip-coating balloon expandable stents mounted on a stainless steel rod in a segmented polyurethane (SPU) solution, and were subsequently subjected to laser-processed microporing (pore diameter, 100 μm; interpore distance, 200 μm). The covered stents, which possessed flat luminal surfaces and micropores that were homogeneously arranged on the whole surface of the covering film, were deployed into the bilateral common carotid arteries of normal New Zealand white rabbits. Angiography after one month of implantation showed all stents were patent with little thrombus formation. The mean thickness of the formed neointimal layers was 292 ± 177 μm (n=8), which was close to the size in non-covered bare stent (231 ± 58 μm, n=7), but markedly decreased (about 2/3) from that in the previously developed wrapping-type covered stents (415 ± 173 μm, P<0.01, n=8). (Int J Artif Organs 2005; 28: 600-8)

KEY WORDS: Stents, Covered stents, Micropore, Flat luminal surface, Drug-eluting

INTRODUCTION

In the treatment of arteriosclerotic stenosis, stent angioplasty, which is much less invasive than conventional surgical treatment, has been widely performed (1-6). However, relatively high rates of in-stent restenosis (20 - 30%) have been observed a few months after stenting and remains an unsolved problem. To reduce restenosis rates, various "second-generation" stents are being developed by incorporating various working principles including surface designs such as polymer coating or fixation (7-15) or immobilization of pharmacological agents (16-30), material designs such as metallics (31, 32) for biocompatibility and biodegradability, and architectural design for flexibility. Recently, drug-eluting stents, such as rapamycin-eluting stents (CYPHER) (33, 34) and taxol-eluting ones (TAXUS) (35-37), have become commercially available, and excellent clinical results have been reported, in which an extremely low restenosis rate in humans has been demonstrated (38).

Covered stents, called stent grafts, have been used in low invasive treatment of diseases in large caliber blood vessels. The use of such stents was first reported in 1991 for the intravascular treatment of aneurysms in the abdominal aorta (39). Recently, this method has been established for percutaneous transluminal angioplasty (PTA) of dilated/constrictive vascular diseases (40, 41). However, for small caliber blood vessels, covered stents made of ePTFE artificial grafts sandwiched between 2 balloon-expandable stents are only clinically available for dissecting cardiovascular diseases (42, 43). Previously, we developed covered stents prepared by wrapping a

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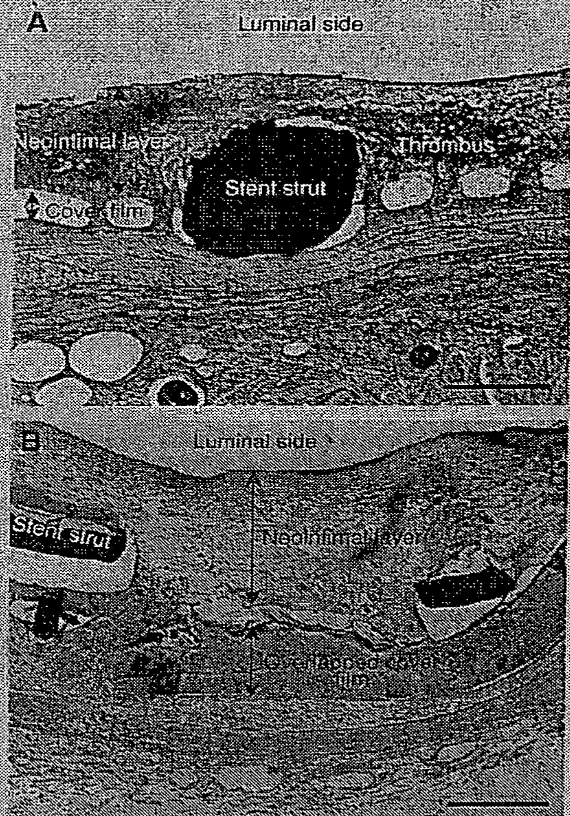


Fig. 1 - (A) *Thrombus formed at the side of the stent strut on the luminal surface of the covered film after 1 week of implantation of the wrapping-typed covered stents into rabbit common carotid artery. Hematoxylin Eosin staining. Bar = 100 µm.* (B) *The film overlapped region in the covering process for the preparation of the wrapping-typed covered stents. The stent was implanted into rabbit common carotid artery for 3 months, during which transluminal tissue in-growth through micropores was completely prevented due to sealing of the micropores. Elastica Van Gieson staining. Bar = 100 µm.*

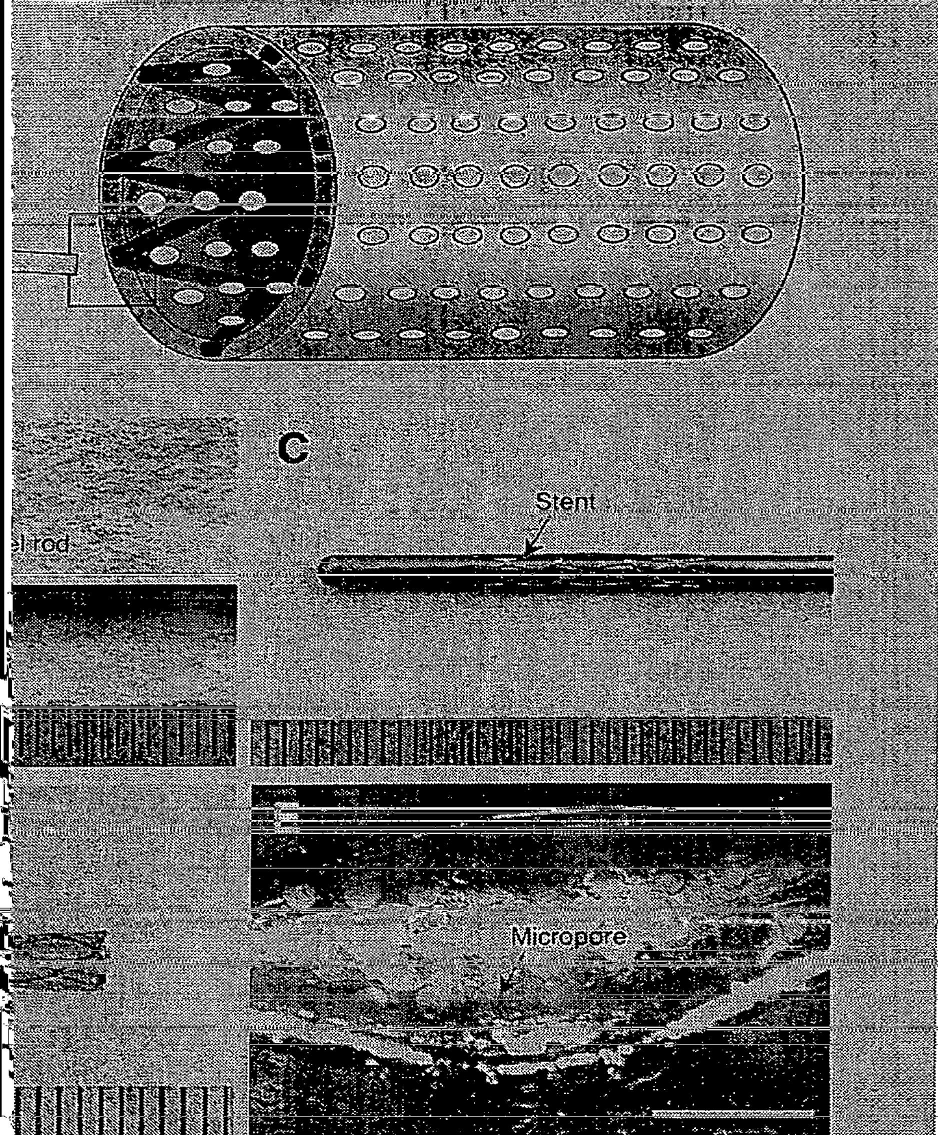
microporous elastomeric film over the stent strut for PTA of arteriosclerotic stenosis (44-46) and occlusion of carotid aneurysms (47). The covered stents were prepared by wrapping balloon-expandable stents in a microporous SPU film, fixing one end of the film to the stent strut by suturing, overlapping the other end of the film with the fixed end, and adhering both ends together by gluing with DMF. In the covered stent, tissue ingrowth into the stent lumen through the stent meshwork would be limited or physically blocked by the cover film. In addition, the cover material was also able to serve as a pharmacological reservoir for drug-eluting. However, such wrapping-type stents have two major disadvantages. The first is in the structural design of the cover. It is known that thrombus formation depends markedly on the superficial geometry of the material surface, and unevenness at the microscopic level on the surface could cause thrombus formation (48-50). Therefore, thrombus generated easily around the strut projecting from the lumen of the cover film into the blood flow immediately after implantation (Fig. 1A). In thrombus, platelet-derived growth factor (PDGF) secreted from aggregated platelets is a potent mitogenic substance for smooth muscle cells (SMCs), which can trigger intimal hyperplasia. The second disadvantage is in the method used to secure the covering film. Since both ends of the film overlapped and were glued to prepare the tube, almost all of the micropores at the glued region were sealed (Fig. 1B). Appropriate microporing at this sealed region is an essential factor for improved early endothelialization and arterial tissue regeneration (51). Indeed, in our previous study, the covered stents showed that no or low micropore density in the covering film resulted in the formation of a thick neo-intimal hyperplasia layer in addition to extreme thrombus formation (44).

In this paper, in order to reduce the above mentioned two disadvantages, a novel preparation method for creating the covered stents using dip-coating was developed. This could provide a flat luminal surface and homogenous micropore arrangement across the whole surface of the cover film. The applicability of the covered stents as a drug-eluting device and an embolization device for aneurysms is discussed.

EXPERIMENTAL SECTION

Preparation of covered stents

A tetrahydrofuran solution containing 5 wt % of SPU (Miractran, Japan Miractran, Kanagawa, Japan) was dip-coated onto a stainless steel rod (2 mm in diameter, 100 mm in length) up to 50 mm from the end and air-dried to form a SPU tube on the rod with a thickness of around 20 µm (Fig. 2B). The SPU-coated rod was mounted with an balloon expandable stainless steel stent (Palmaz-Schatz stent, length: 15 mm, diameter: 1.2 mm, Johnson & Johnson KK, Tokyo, Japan) at the center of the SPU



sign of the novel microporous covered stents. The photographs show each step in the fabrication steel rod was firstly dipped into a segmented polyurethane (SPU) solution to fabricate a SPU tube ounting of the balloon-expandable stent on the SPU coated rod (B) and over-coating the stent- dipping process (C). Thereafter microporing the SPU film with ablation using an excimer laser was overed stent from the rod (E). Micropores are homogeneously arranged on the whole surface of the uried to provide smooth luminal surface.

coated region and over-coated with the SPU solution by further dipping. The total thickness of the SPU film was around 50 μm. The SPU film, buried within the stent, was micropored using a KrF excimer laser apparatus (L4500, Hamamatsu Photonics, Shizuoka, Japan) (Fig. 2C). The pore diameter was fixed at 100 μm and the interpore distance was fixed at 200 μm. After microprocessing, the rod was removed to obtain a microporous SPU-covered stent.

Implantation

The experimental animals were New Zealand white rabbits, weighing 2 to 3 kg (n=8 for two types of covered stents and n=7 for non-covered bare stents). The experiments were performed according to the "Principles of Laboratory Animal Care" (formulated by the National Society for Medical Research) and the "Guide for the Care and Use of Laboratory Animals" (National Institutes of Health Publication, No. 56-23, revised 1985). The rabbits were anesthetized with a mixture of ketamine (62.5 mg/kg) and xylazine (8.3 mg/kg). Heparin (2000 IU) was administered only during angiography. The covered stent mounted on a PTA balloon catheter (3.0 mm, 2 cm, SAVVY, Johnson & Johnson) was positioned into the common carotid artery (approximately 3 mm) from the femoral artery through a 5F sheath introducer under fluoroscopy using a standard PTA micro-guide wire. The balloon was inflated to a pressure of 8 atm for 30 seconds, deflated, and then slowly withdrawn, leaving the covered stent in place. Neither anti-platelet agents nor additional anti-coagulants were administered during the one-month follow-up period.

Microscopic examination

One month after stenting, animals were anesthetized and a pre-euthanasia angiogram of their common carotid arteries was conducted, followed by euthanasia and perfusion-fixation. The stented arteries were dissected free, fixed with 10% formaldehyde in phosphate buffer (pH 7.4) for at least 48 hours. Specimens for light microscopy were dehydrated in a graded alcohol series and embedded in glycolmethacrylate. Thin sections of the tissues were prepared in the direction of the circumference, subjected to standard hematoxylin and eosin staining and then observed under light microscopy (E1000M, Nikon, Tokyo, Japan). Specimens for SEM were post-fixed with 1% osmium tetraoxide after formaldehyde fixation, dehydrated in a graded series of ethanol, critical point dried, and then sputter-coated with platinum. The surfaces of longitudinally cut stents were observed using a scanning electron microscope (SEM: JSM-6301, JEOL, Tokyo, Japan).

RESULTS

Covering of stents

The structural design of the developed microporous covered stents is illustrated in Figure 2A. The stents were fabricated as follows. First, a SPU tube, buried within a stent, was prepared by dip-coating (Fig. 2B) using a stainless steel rod as a mold (Fig. 2C).

Then, microporing of the covered film was performed using a previously developed excimer laser ablation technique (Fig. 2C). An excimer laser is a powerful source of pulsed monochromatic ultraviolet light. When condensed laser pulses fall on a polymer surface, breaking of numerous chemical bonds occurs in the polymer resulting in the formation of a micropore (52). The obtained covered stents had homogeneous micropore arrangements, in which the pore diameter was 100 μm and the interpore distance was 200 μm (Fig. 2E). In addition, since the stent strut was buried into the SPU covered film, the inner surface of the covered stent was flat.

The covered stent obtained was then mounted on a commercially available PTA balloon-expandable catheter using a hand crimping device. No crinkling or rupturing of the cover film occurred, even when the covered stent was dilated up to 3 mm from 2 mm in diameter by expanding the balloon with pressurized water. No differences in dilation of the stent were noted irrespective of the presence of covering. After balloon deflation and subsequent removal of the balloon catheter, the stent maintained its shape and showed no shrinkage (Fig. 2D).

In vivo *performance*

The microporous covered stents, mounted on PTA balloon-expandable catheters, were navigated and placed into the bilateral common carotid arteries of rabbits via the femoral arteries under fluoroscopy. Manipulation of the covered stents in the blood vessels was smooth with no handling differences found, irrespective of the presence of

covering. Previously developed covered stents, which were prepared by wrapping, were used as a control.

After one month of implantation, angiographs of all the stents showed patent with no significant intimal hyperplasia observed in the dip-coating-type stents (Fig. 3A). In addition, SEM observations indicated that the surfaces of the stents were fully covered with confluent endothelial cells (Fig. 3B). The endothelial cells on all of the luminal surfaces exhibited a normal spindle shape and the direction of cellular elongation was parallel to that of the blood flow. Histological evaluation showed that in the control group (wrapping-type stents), intensive thrombus formation at the luminal surface of the covering film, particularly at the side of the strut, and neointimal hyperplasia occurred and was similar to results obtained in our previous study, as shown in Figure 1. In contrast, in the dip-coated-type stents, a relatively thin neointimal layer formed similar to the case of non-covered bare stents. In addition, little thrombus formation was observed on the luminal surface of the covering film (Fig. 3A). The mean thickness of the neointimal layer, which was close to the value in the bare stents (231 ± 58 μm), was 292 ± 177 μm.

These values were approximately 2/3 of that of the previously developed wrapping-type covered stents (415 ± 173 μm and 50 ± 7%, P<0.01).

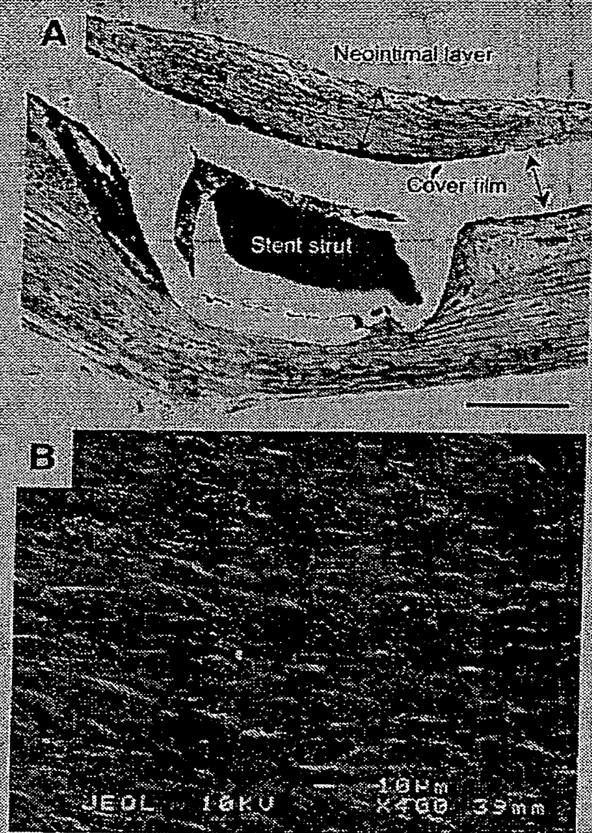


Fig. 3 - Light micrograph of circumference section after Hematoxylin Eosin staining **(A)** *and scanning electron micrographs (SEM) of the luminal surface* **(B)** *of the rabbit common carotid artery after 1-month of implantation of the dipcoated-typed covered stents with smooth luminal surface. Bar = 50 μm in (A).*

DISCUSSION

As next generation stents, we have developed stents covered with a microporous polymeric film, which provides a physical barrier against cell in-growth, and a reservoir for drug-eluting for the prevention of restenosis (44-46). On the surface of the film a large amount of drugs can be retained compared to the strut alone.

In this study, to increase *in vivo* biological reliability, including blood and tissue compatibilities, of the covered stents, a dip-coating method for the covering process was newly developed. Using this method, whole covering of the struts with SPU tube and flat luminal surface was provided. Even after covering there was little difference in expansion ability by dilation with a balloon catherter. In our previous study, when the wrapping-type covered stents were implanted in rabbit carotid arteries thrombus formation was often observed around the struts on the cover film. This may be caused by impaired blood flow due to projection of the strut from the luminal surface of the cover film into the blood flow.

On the contrary, few thrombus were formed on the flat luminal surface in the dip-coating type stents, which was observed in this study.

The thickness of the neointimal layer was enhanced on the low porous cover film surface in our previous study (44). Irrespective of the presence of the stent cover, the formation of the neointimal layer was usually maximum at about one month after stent deployment in carotid arteries of normal rabbits, which may have been due to tissue injury or inflammation (44-46). However, a stent implantation period of longer than one month resulted in a

reduced thickness of the neointimal layer by the normal wound healing process, which was much different from the clinical course of intimal hyperplasia in human arteriosclerotic restenosis as described in the introduction section. Therefore, in this study the implantation period was fixed at one month. In the dip-coating type stents the neointimal layer formed was markedly decreased from that in the wrapping type stents, whose thickness was similar to that of the non-covered bare stents. It was suggested that the flat luminal surface prevented polymer-triggered, inflammation-induced thickening of the neointimal layer. Therefore, it can be said that the optimal design of the framework of the covered stents is well established.

Since the stents developed here have a cover film, they can be used for embolization devices for aneurysms in small caliber blood vessels (47). Currently, neuro-intervention using platinum coils is used for the treatment of cervical and carotid siphon aneurysms.

With the covered stents, embolization of relatively large aneurysms can be safely and reliably performed by deployment of a single device.

As described above, drug immobilization on the cover film of the covered stents may be a powerful tool to prevent the formation of the neointimal layer in addition to the surface geometrical design. Using the cover film as a platform for drug immobilization, different drugs with optimal purposes for the blood-contacting inner surface, and the vascular tissue-contacting outer one of the cover film, can be retained (46). In our recent study, heparin, expected to markedly suppress thrombus formation, and FK506 (tacrolimus) (46, 53, 54), expected to reduce inflammation, were immobilized on respective inner or outer surface of the cover stents fabricated by the dip-coating method. Upon implantaion of the drug-eluting covered stents with differential drug coating, a very thin neointimal layer was regenerated after one month. The thin layer thickness was maintained up to three months after implantaion. In addition to the surface geometrical design, optimal drug immobilization such as statin (55, 56) will greatly increase the reliability of the stents for prevention of restenosis. This is now being evaluated using an animal model under conditions more directly resembling clinical applications such as using hyperlipidemia rabbits with an intimal hypertrophy produced by balloon injury.

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